Cosmeceutical Critique

Apigenin

Apigenin (5,7,4'-trihydroxyflavone) is a low-toxic, nonmutagenic plant flavonoid that is widely found in herbs (endive, clove, and German chamomile), fruit (apples, cherries, and grapes), beverages (tea and wine), vegetables (beans, broccoli, celery, leeks, onions, barley, parsley, and tomatoes), and propolis (Skin Pharmacol. Appl. Skin Physiol. 2002;15:297-306; Eur. J. Cancer 1996;32A:146-51; J. Cell Biochem. [Suppl.] 1997;28-9:39-48).

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Apigenin shows promising chemopreventive activity against skin cancer (J. Pharm. Sci. 1997;86:721-5) and has demonstrated anti-inflammatory properties (Skin Pharmacol. Appl. Skin Physiol. 2001;14:373-85). It is also believed to be partly responsible for the soothing, antispasmodic, anxiolytic activity that has been attributed to chamomile (Planta Medica 1995;61:213-6).

Antitumor Actions in Animals

In a series of studies conducted almost 2 decades ago, the topical application of apigenin to Sencar mice inhibited, in a dose-dependent manner, skin tumorigenesis initiated by 7,12-dimethylbenz[*a*]anthracene (DMBA) and promoted by 12-*O*-tetradecanoylphorbol-13-acetate (TPA). In the first study, 48% of DMBA/TPA–treated mice developed carcinomas by 33 weeks after DMBA initiation, but no carcinomas occurred in the DMBA/apigenin/TPA–treated groups. In the second study, apigenin prolonged the latency period of papilloma formation by 3 weeks and dose dependently reduced papilloma incidence. Apigenin also significantly inhibited carcinoma incidence and reduced the number of tumors. In addition, the researchers concluded that apigenin exhibited the tendency to reduce conversion of papillomas to carcinomas (Cancer Res. 1990;50:499-502).

Several studies conducted since then established that the topical application of apigenin inhibits UV-induced skin tumorigenesis in mouse skin (Mol. Carcinog. 2002;33:36-43; Carcinogenesis 1996;17:2367-75; Mol. Carcinog. 1997;19:74-82). Apigenin also has been shown to suppress TPA-mediated tumor promotion in mouse skin, partly because of its inhibitory effects on protein kinase C and expression of c-Jun and c-Fos (Eur. J. Cancer 1996;32A:146-51).

In addition to its ability to inhibit tumors, apigenin has been noted for its in vitro antioxidant properties against the superoxide anion and peroxyl radicals. In a study performed 15 years ago, the compound demonstrated anti-inflammatory activity in rats. Intradermal application of liposomal apigenin-7-glucoside dose-dependently inhibited skin inflammation previously induced by injection of xanthine oxidase and cumene hydroperoxide (Arzneimittelforschung 1993;43:370-2).

Researchers who studied the effects of apigenin using the mouse keratinocyte 308 cell line, which contains a wild-type p53 gene, determined that the compound may exert antitumorigenic activity by stimulating the p53-p21/waf1 response pathway (Carcinogenesis 2000;21:633-9).

In another study of apigenin's inhibitory influence on skin tumorigenesis, investigators found, using DNA flow cytometric analysis, interruptions in the cell cycle. Keratinocytes cultured for 24 hours in apigenin-containing medium induced a G2/M arrest in two mouse skin–derived cell lines, C50 and 308, and in human HL-60 cells. This effect was fully reversible after an additional 24 hours in apigenin-free medium (Carcinogenesis 1996;17:2367-75).

Subsequent research from the same laboratory provided evidence that apigenin can induce G1 arrest in human diploid fibroblasts by inhibiting cyclin-dependent kinase 2 (cdk2) activity and phosphorylation of retinoblastoma protein, and by inducing the cdk inhibitor p21/waf1.

These activities, the researchers wrote, may mediate the flavonoid's in vivo chemopreventive activities (Mol. Carcinog. 1997;19:74-82).

The preponderance of research on this botanical antioxidant points toward anticarcinogenic activity. In a study evaluating 15 flavonoids for their effects on morphologic changes in soft agar and cellular growth in v-H-ras–transformed NIH3T3 cells, only apigenin, kaempferol, and genistein had a reversing effect on the transformed morphology of these cells. The researchers concluded that the suppression of protein kinase C activity and nuclear oncogene expression might contribute to the molecular mechanism of action exhibited by apigenin (as well as curcumin) in its inhibition of TPA-induced tumor promotion (J. Cell Biochem. [Suppl.] 1997;28-9:39-48).

Other authors have expressed optimistism that apigenin will show a broad spectrum of chemopreventive effects by influencing various molecular targets that affect pathways in the cell (J. Nutr. 2003;133:3800S-4S).

Alternative Sunscreen?

In a study aimed at ascertaining the efficacy of apigenin as a chemopreventive agent against UV-induced skin cancer as well as DNA damage in a cell-free system, investigators found that apigenin treatment from 12 hours before and until 1 hour after UVA/B exposure inhibited 25%-45% of ornithine decarboxylase activity. Further, apigenin treatment of SKH-1 mouse skin before each UVB exposure lowered cancer incidence (52% inhibition) and increased tumor-free survival, compared with control mice (Anticancer Res. 1997;17:85-91).

Of particular interest related to several promising studies is the speculation among some authors that apigenin may represent an alternative sunscreen agent for humans (Mol. Carcinog. 1997;19:74-82; Carcinogenesis 1996;17:2367-75).

For an apigenin formulation to prevent skin cancer, though, it has been determined that the apigenin must be delivered into viable epidermis (Pharm. Res. 1996;13:1710-5). In vivo skin penetration studies of the flavonoids apigenin, luteolin, and apigenin 7-*O*-β-glucoside demonstrated several years ago that the compounds were adsorbed at the skin surface, but also penetrated into deeper layers (Pharmazie 1994;49:509-11).

Down the Road

The stage may be set for apigenin to be included in formulations, because, in addition to the expanding body of evidence indicating its anticarcinogenic properties, recent work has shown apigenin's potential as an antiphotoaging agent.

Researchers focusing on identifying antiphotoaging compounds assessed the antioxidative activity and inhibitory effects on matrix metalloproteinase-1 (MMP-1) of the extracts of a marine plant, *Zostera marina* L. These extracts contained apigenin-7-*O*-β-D-glucoside, chrysoeriol, and luteolin. All of the compounds were found to scavenge the 1,1-diphenyl-2-picrylhydrazyl radical and the superoxide radical. These botanical constituents are deemed to have antioxidative activity and inhibitory effects on MMP-1 expression, and are considered promising targets for inclusion in antiphotoaging formulations (Arch. Pharm. Res. 2004;27:177-83).

Conclusions

The great upsurge in research and interest in plant polyphenols in recent years has been characterized by greater understanding of these compounds' potential health benefits. The body of research on the phenolic flavonoid apigenin is relatively small, with the preponderance of data accumulating in the past 15 years.

Apigenin is found in German chamomile and is most likely to be included in dermatologic products featuring chamomile. It is also an active ingredient in propolis.

With its promising research profile indicating anticarcinogenic and antiphotoaging effects, in vitro and in vivo, much more research regarding this potent antioxidant is likely and warranted. ■

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Expert Favors Proven Agents Over Peptide Cosmeceuticals

BY TIMOTHY F. KIRN
Sacramento Bureau

Las Vegas — Dermatologists should tell their patients to be skeptical of "peptide" cosmeceuticals and to stick with proven agents, Dr. Kathy A. Fields said at the annual meeting of the American Society of Cosmetic Dermatology and Aesthetic Surgery.

Agents such as palmitoyl pentapeptide-3 have been shown to stimulate collagen production in a skin culture, but as with so many cosmeceutical products, none of the peptides has been proven to be effective in a published clinical trial or has any compelling scientific data, said Dr. Fields, a dermatologist in San Francisco who is a coinventor of Proactiv Solution, the popular acne treatment, and has her own line of cosmeceuticals, Rodan + Fields.

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The peptides in cosmeceuticals may or may not penetrate the stratum corneum to any great degree, and they need to reach the dermis to be taken up by cells to have their effects.

"They don't last long," she said of the cosmeceutical peptides. "When you apply them on the skin, they go away rapidly. So they either don't penetrate or if they do, they may not have enough time or enough concentration to get to the target organs to make collagen."

Peptide-containing cosmeceuticals can also cost a lot, Dr. Fields said. StriVectin-SD, for example, costs about $135 for a 6-ounce tube when purchased from the manufacturer, and it contains palmitoyl pentapeptide as a reported active ingredient.

There is also little need for a patient interested in a skin rejuvenating regimen to use a peptide product because there are proven agents such as α-hydroxy acids and salicylic acid, and retinoids such as tretinoin and retinol.

Those are the agents she recommends to patients. "I love the old technology," she said.

If a patient does not tolerate a retinoid or one of the other older agents, she tells them to just use it twice a week to get started, rather than switch to a product that may be dubious. The patient can probably work up to using it more often. ■